CLAIMS

What is claimed is:

1. A synthetic oligomeric compound which is specifically hybridizable with a preselected RNA target and comprises;

a first segment having at least one ribofuranosyl nucleoside subunit which is modified to improve the binding affinity of said compound to the preselected RNA target when compared to the binding affinity of an unmodified oligoribonucleotide to the RNA target; and

a second segment comprising at least four consecutive ribofuranosyl nucleoside subunits having 2'-hydroxyl moieties thereon;

said nucleoside subunits of said oligomeric compound being connected by internucleoside linkages which are modified to stabilize said linkages from degradation as compared to phosphodiester linkages.

2. The oligomeric compound of claim 1 further comprising a third segment comprising at least one ribofuranosyl nucleoside subunit which is modified to improve the binding affinity of said compound to the preselected RNA target when compared to the binding affinity of an unmodified oligoribonucleotide to the RNA target.

3. The oligomeric compound of claim 1 which, when hybridized with said RNA target, is capable of activating a double-stranded RNAse enzyme to effect cleavage of said RNA target.

4. The oligomeric compound of claim 2 wherein said second segment is positioned between said first and said third segments.

5. The oligomeric compound of claim 2 wherein each of

said first and third segments comprise at least three subunits.

6. The oligomeric compound of claim 2 wherein said second segment comprises from four to twelve nucleoside subunits.

7. The oligomeric compound of claim 6 wherein said second segment comprises from five to nine nucleoside subunits.

8. The oligomeric compound of claim 2 wherein said second segment has at least five subunits and said first and third segments each have at least three subunits.

9. The oligomeric compound of claim 8 wherein said second segment has at least seven nucleoside subunits.

10. A synthetic oligomeric compound which is specifically hybridizable with a preselected RNA target and comprises;

a first segment having at least one ribofuranosyl nucleoside subunit that is modified to improve at least one of: pharmacokinetic binding, absorption, distribution or clearance properties of the compound; affinity or specificity of said compound to said target RNA; or modification of the charge of said compound as compared to unmodified compound; and

a second segment comprising at least four consecutive ribofuranosyl nucleoside subunits having 2'-hydroxyl moieties thereon;

said nucleoside subunits of said oligomeric compound being connected by internucleoside linkages which are modified to stabilize said linkages from degradation as compared to phosphodiester linkages.

11. The oligomeric compound of claim 10 further comprising a third segment comprising at least one ribofuranosyl nucleoside subunit that is modified to improve at least one of: pharmacokinetic binding, absorption, distribution or clearance properties of the compound; affinity or specificity of said compound to said target RNA; or modification of the charge of said compound as compared to unmodified compound.

12. The oligomeric compound of claim 10 which, when hybridized with said RNA target, is capable of activating a double-stranded RNAse enzyme to effect cleavage of said RNA target.

13. The oligomeric compound of claim 11 wherein said second segment is positioned between said first and said third segments.

14. The oligomeric compound of claim 11 wherein each of said first and third segments comprise at least three subunits.

15. The oligomeric compound of claim 11 wherein said second segment comprises from four to twelve nucleoside subunits.

16. The oligomeric compound of claim 15 wherein said second segment comprises from five to nine nucleoside subunits.

17. The oligomeric compound of claim 11 wherein said second segment has at least five subunits and said first and third segments each have at least three subunits.

18. The oligomeric compound of claim 17 wherein said second segment has at least seven nucleoside subunits.

19. A synthetic oligomeric compound which is specifically hybridizable with a preselected RNA target comprising;

a first segment having at least one 2'-O-C_{1-20} alkyl, 2'-O-substituted C_{1-20} alkyl or 2'-fluoro modified ribofuranosyl nucleoside subunit where the substitution on said alkyl is amino, hydroxy or C_{1-10} alkyl ether modification;

a second segment comprising at least four consecutive ribofuranosyl nucleoside subunits having 2'-hydroxyl moieties thereon; and

said nucleoside subunits of said oligomeric compound being connected by internucleoside linkages that are stable to degradation as compared to phosphodiester bonds.

20. The oligomeric compound of claim 19 further comprising a third segment comprising at least one 2'-O-C_{1-20} alkyl, 2'-O-substituted C_{1-20} alkyl or 2'-fluoro modified ribofuranosyl nucleoside subunit where the substitution on said alkyl is amino, hydroxy or C_{1-10} alkyl ether.

21. The oligomeric compound of claim 20 wherein said second segment is positioned between said first and said third segments.

22. The oligomeric compound of claim 20 wherein each of said first and third segments comprise at least three subunits.

23. The oligomeric compound of claim 20 wherein said second segment comprises from four to twelve nucleoside subunits.

24. The oligomeric compound of claim 20 wherein said second segment comprises from five to nine nucleoside subunits.

25. The oligomeric compound of claim 20 wherein said second segment has at least five subunits and said first and third segments each have at least three subunits.

26. The oligomeric compound of claim 20 wherein said second segment has at least seven nucleoside subunits.

27. The oligomeric compound of claim 19 which, when hybridized with said RNA target, is capable of activating a double stranded RNAse enzyme to effect cleavage of said RNA target.

28. The oligomeric compound of claim 22 wherein each of said ribofuranosyl nucleoside subunits of said first and said third segments is modified to include a 2'-O-C_{1-20} alkyl, 2'-O-substituted C_{1-20} alkyl or 2'-fluoro and wherein the substitution on said alkyl is amino, hydroxy or C_{1-10} alkyl ether.

29. The oligomeric compound of claim 19 wherein at least two of said nucleoside subunits are connected by a phosphorothioate, 3'-deoxy-3'-thio-phosphorothioate, 5'-deoxy-5'-thio-phosphorothioate, phosphorodithioate, phosphoroselenate, 3'-deoxy phosphinate, 5'-deoxy phosphinate, borano phosphate, 3'-deoxy-3'-amino phosphoramidate, 5'-deoxy-5'-amino phosphoramidate, hydrogen phosphonate, borano phosphate ester, phosphoramidate, alkyl phosphonate, aryl phosphonate or phosphotriester linkage.

30. The oligomeric compound of claim 19 wherein each of the nucleoside subunits of said first segment are connected by phosphorothioate, 3'-deoxy-3'-thio-phosphorothioate, 5'-deoxy-5'-thio-phosphorothioate, phosphorodithioate, phosphoroselenate, 3'-deoxy phosphinate, 5'-deoxy phosphinate, borano phosphate, 3'-deoxy-3'-amino phosphoramidate, 5'-deoxy-5'-amino phosphoramidate, hydrogen phosphonate, borano phosphate ester, phosphoramidate, alkyl

phosphonate, aryl phosphonate or phosphotriester linkages.

31. The oligomeric compound of claim 19 wherein each of said nucleoside subunits of said first segment are connected by phosphorothioate linkages.

32. The oligomeric compound of claim 19 wherein each of said nucleoside subunits of said second segment are connected by phosphorothioate linkages.

33. The oligomeric compound of claim 20 wherein each of said nucleoside subunits of said third segment are connected by phosphorothioate, 3'-deoxy-3'-thio-phosphorothioate, 5'-deoxy-5'-thio-phosphorothioate, phosphorodithioate, phosphoroselenate, 3'-deoxy phosphinate, 5'-deoxy phosphinate, borano phosphate, 3'-deoxy-3'-amino phosphoramidate, 5'-deoxy-5'-amino phosphoramidate, hydrogen phosphonate, borano phosphate ester, phosphoramidate, alkyl phosphonate, aryl phosphonate or phosphotriester linkages.

34. The oligomeric compound of claim 20 wherein each of said nucleoside subunits of said third segment are connected by phosphorothioate linkages.

35. The oligomeric compound of claim 20 wherein each of said nucleoside subunits of said first, said second and said third subunits are connected by phosphorothioate linkages.

36. The oligomeric compound of claim 19 wherein each of the nucleoside subunits of said first segment are connected by carbonate, carbamate, silyl, sulfur, sulfonate, sulfonamide, formacetal, thioformacetal, oxime, methyleneimino, methylenemethylimino, methylenehydrazo, methylenedimethylhydrazo, methyleneoxymethylimino or methylenecarbonylamino linkages.

37. The oligomeric compound of claim 20 wherein each of the nucleoside subunits of said third segment are connected by carbonate, carbamate, silyl, sulfur, sulfonate, sulfonamide, formacetal, thioformacetal, oxime, methyleneimino, methylenemethylimino, methylenehydrazo, methylenedimethylhydrazo, methyleneoxymethylimino or methylenecarbonylamino linkages.

38. A synthetic oligomeric compound which is specifically hybridizable with a preselected RNA comprising at least twelve ribofuranosyl nucleosides in a sequence;

said nucleoside subunits being joined by internucleoside bonds which are more stable to degradation as compared to phosphodiester bonds;

the compound having two wing portions interspaced by a gap portion;

the wing portions each comprising at least one modified nucleoside subunit, which modified nucleoside subunit is modified to improve at least one of: pharmacokinetic binding, absorption, distribution or clearance properties of the compound; affinity or specificity of said compound to said target RNA; or modification of the charge of said compound as compared to unmodified compound;

the gap portion having at least four consecutive ribonucleoside subunits.

39. The oligomeric compound of claim 38 wherein said gap portion has at least five consecutive ribonucleoside subunits.

40. A synthetic oligomeric compound comprising, in sequence;

a first segment having a plurality of 2'-O-alkyl nucleoside subunits;

a second segment having at least four consecutive 2'-hydroxyl ribonucleoside subunits; and

a third segment having a plurality of 2'-O-alkyl

nucleoside subunits; and

the nucleoside subunits of the oligomer being joined by phosphorothioate internucleoside linkages.

41. The oligomeric compound of claim 40 wherein said second segment has at least five consecutive 2'-hydroxyl ribonucleotide subunits.

42. The oligomeric compound of claim 40 wherein said oligomer is specifically hybridizable with a preselected RNA.

43. A method for specifically cleaving a preselected RNA comprising contacting said RNA with an oligomeric compound comprising at least twelve ribofuranosyl nucleosides subunits in a sequence which is specifically hybridizable with said preselected RNA;

said nucleoside subunits being joined by internucleoside bonds which are more stable to degradation as compared to phosphodiester bonds;

the compound having at least one segment comprising at least one modified nucleoside subunit, which modified nucleoside subunit is modified to improve at least one of: pharmacokinetic binding, absorption, distribution or clearance properties of the compound; affinity or specificity of said compound to said target RNA; or modification of the charge of said compound as compared to an unmodified compound;

said compound having a further segment having at least four consecutive 2'-hydroxyl ribonucleoside subunits.

44. The method of claim 43 wherein said further segment has at least five consecutive ribonucleoside subunits.

45. A method for treating an organism having a disease characterized by the undesired production of a protein

comprising contacting the organism with an oligomeric compound of the invention having a sequence of nucleoside subunits capable of specifically hybridizing with a complementary strand of ribonucleic acid with at least one of the nucleoside subunits being modified to improve at least one of: pharmacokinetic binding, absorption, distribution or clearance properties of the compound; affinity or specificity of said compound to said target RNA; or modification of the charge of said compound as compared to unmodified compound; a plurality of the nucleoside subunits being located in a consecutive sequence and having 2'-hydroxyl-pentofuranosyl sugar moieties.

46. A compositions including a pharmaceutically effective amount of an oligomeric compound in a pharmaceutically acceptable diluent or carrier, said oligomeric compound comprising a sequence of nucleoside subunits capable of specifically hybridizing with a complementary strand of RNA wherein a plurality of the nucleoside subunits of the oligomeric compound are modified to improve at least one of: pharmacokinetic binding, absorption, distribution or clearance properties of the compound; affinity or specificity of said compound to said target RNA; or modification of the charge of said compound as compared to an unmodified compound; wherein a further plurality of the nucleoside subunits have 2'-hydroxyl-pentofuranosyl sugar moieties.

47. A method for *in vitro* modification of a sequence-specific target RNA comprising contacting a test solution containing a dsRNase enzyme and said target RNA with an oligomeric compound having a sequence of nucleoside subunits capable of specifically hybridizing to said target RNA where at least one of the nucleoside subunits is modified to improve the affinity or specificity of said compound to said target RNA; and where a plurality of the nucleoside subunits have 2'-hydroxyl-pentofuranosyl sugar moieties.

48. A method of concurrently enhancing hybridization and dsRNase enzyme activation in an organism comprising contacting the organism with an oligomeric compound having a sequence of nucleoside subunits capable of specifically hybridizing to a complementary strand of target RNA, where at least one of the nucleoside subunits is modified to improve at least one of: pharmacokinetic binding, absorption, distribution or clearance properties of the compound; affinity or specificity of said compound to said target RNA; or modification of the charge of said compound as compared to unmodified compound; wherein a plurality of the nucleoside subunits have 2'-hydroxy-pentofuranosyl sugar moieties.

49. A synthetic oligomeric compound which is specifically hybridizable with a preselected RNA target comprising;

a first segment including at least one surrogate nucleoside subunit;

a second segment comprising at least four ribofuranosyl nucleoside subunits located in a consecutive sequence and having 2'-hydroxyl moieties thereon; and

said nucleoside subunits of said oligomeric compound being connected by internucleoside linkages that are stable to degradation as compared to phosphodiester bonds.

50. The oligomeric compound of claim 49 wherein said surrogate nucleoside subunit is a peptide nucleic acid subunit.

51. The oligomeric compound of claim 49 wherein said surrogate nucleoside subunit is a morpholino nucleoside subunit.

52. The oligomeric compound of claim of 49 wherein said surrogate nucleoside is a cyclobutyl nucleoside.

53. The oligomeric compound of claim 49 wherein said surrogate nucleoside is a pyrrolidine nucleoside.

54. A synthetic oligomeric compound which is specifically hybridizable with a preselected RNA target comprising;

a first segment including at least two nucleoside subunits;

said nucleoside subunits of said first segment being connected by non-phosphorus internucleoside linkages;

a second segment comprising at least four consecutive ribofuranosyl nucleoside subunits having 2'-hydroxyl moieties thereon; and

said nucleoside subunits of said second segment being connected by internucleoside linkages that are stable to degradation as compared to phosphodiester bonds.

55. The oligomeric compound of claim 54 wherein said non-phosphorous linkages are carbonate, carbamate, silyl, sulfur, sulfonate, sulfonamide, formacetal, thioformacetal, oxime, methyleneimino, methylenemethylimino, methylene-hydrazo, methylenedimethylhydrazo or methyleneoxymethylimino, methylenecarbonylamino internucleoside linkages.

56. The oligomeric compound of claim 54 wherein said non-phosphorus internucleoside linkages are formacetal, thioformacetal, methylenemethylimino, methylenedimethyl-hydrazo, methyleneoxymethylimino or methylenecarbonylamino internucleoside linkages.

57. The oligomeric compound of claim 54 said nucleoside subunits of said second segment being connected by phosphoro-thioate internucleoside linkages.

58. A synthetic oligomeric compound which is specifically hybridizable with a preselected RNA target

comprising;

a first segment including at least three nucleoside subunits;

said nucleoside subunits of said first segment being connected by alternating phosphorus, non-phosphorus internucleoside linkages;

a second segment comprising at least four consecutive ribofuranosyl nucleoside subunits having 2'-hydroxyl moieties thereon; and

said nucleoside subunits of said second segment being connected by internucleoside linkages that are more stable to degradation as compared to phosphodiester bonds.

59. The oligomeric compound of claim 58 wherein said non-phosphorous linkages are carbonate, carbamate, silyl, sulfur, sulfonate, sulfonamide, formacetal, thioformacetal, oxime, methyleneimino, methylenemethylimino, methylene-hydrazo, methylenedimethylhydrazo or methyleneoxymethylimino, methylenecarbonylamino internucleoside linkages.

60. The oligomeric compound of claim 58 wherein said non-phosphorus internucleoside linkages are formacetal, thioformacetal, methylenemethylimino, methylenedimethyl-hydrazo, methyleneoxymethylimino or methylenecarbonylamino internucleoside linkages.

61. The oligomeric compound of claim 58 wherein said nucleoside subunits of said second segment are connected by phosphorothioate internucleoside linkages.

62. A synthetic oligomeric compound which is specifically hybridizable with a preselected RNA target comprising;

a first segment including at least two nucleoside subunits;

said nucleoside subunits of said first segment being

connected by 3'-deoxy-3'-thio-phosphorothioate, 5'-deoxy-5'-thio-phosphorothioate, phosphorodithioate, phosphoroselenate, 3'-deoxy phosphinate, 5'-deoxy phosphinate, borano phosphate, 3'-deoxy-3'-amino phosphoramidate, 5'-deoxy-5'-amino phosphoramidate, hydrogen phosphonate, borano phosphate ester, phosphoramidate, alkyl phosphonate, aryl phosphonate or phosphotriester phosphate linkages; and

a second segment comprising at least four consecutive ribofuranosyl nucleoside subunits having 2'-hydroxyl moieties thereon; and

said nucleoside subunits of said second segment being connected by internucleoside linkages that are more stable to degradation as compared to phosphodiester bonds.

63. The oligomeric compound of claim 62 including a third segment of at least two nucleoside subunits, said nucleoside subunits of said third segment connected by 3'-deoxy-3'-thio-phosphorothioate, 5'-deoxy-5'-thio-phosphorothioate, phosphorodithioate, phosphoroselenate, 3'-deoxy phosphinate, 5'-deoxy phosphinate, borano phosphate, 3'-deoxy-3'-amino phosphoramidate, 5'-deoxy-5'-amino phosphoramidate, hydrogen phosphonate, borano phosphate ester, phosphoramidate, alkyl phosphonate, aryl phosphonate or phosphotriester phosphate linkages.

64. The oligomeric compound of claim 62 wherein said nucleoside subunits of said first and third segments are connected by phosphorodithioate, phosphoroselenate, 3'-deoxy phosphinate, 3'-deoxy-3'-amino phosphoramidate, phosphoramidate, alkyl phosphonate, aryl phosphonate or phosphotriester phosphate linkages.

65. A synthetic oligomeric compound which is specifically hybridizable with a preselected RNA target and comprises;

a first segment having at least one ribofuranosyl

nucleoside subunit that is not a DNA or RNA major building block nucleoside;

a second segment comprising at least four consecutive ribofuranosyl nucleoside subunits having 2'-hydroxyl moieties thereon;

said nucleoside subunits of said oligomeric compound being connected by internucleoside linkages which are modified to stabilize said linkages from degradation as compared to phosphodiester linkages.

66. The compound of claim 65 wherein said first segment nucleoside subunit is selected from nucleosides having xanthine, hypoxanthine, 2-aminoadenine, 6-alkyl derivatives of adenine and guanine, 2-alkyl derivatives of adenine and guanine, 7-alkyl derivatives of adenine and guanine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 2 thio uracil and cytosine, 8-halo, amino, thiol, thioalkyl, hydroxyl adenine and guanine, and 5-trifluoromethyl uracil and cytosine, as their heterocyclic base.

67. A synthetic oligomeric compound which is specifically hybridizable with a preselected RNA target and comprises;

a first segment having at least one ribofuranosyl nucleoside subunit excluding the nucleoside group consisting of adenosine, 2'-deoxyadenosine, guanosine, 2'-deoxyguanosine, cytidine, 2'-deoxycytidine, uridine and 2'-deoxythymidine;

a second segment comprising at least four consecutive ribofuranosyl nucleoside subunits having 2'-hydroxyl moieties thereon;

said nucleoside subunits of said oligomeric compound being connected by internucleoside linkages which are modified to stabilize said linkages from degradation as compared to phosphodiester linkages.

68. A mammalian ribonuclease having the activity of catalyzing the degradation of a double stranded substrate wherein one of said strands of said substrate is a mRNA and the other of said strands of said substrate comprises a compound having in sequence a first segment comprising a plurality of 2' modified nucleoside subunits and a second segment comprising at least four consecutive ribofuranosyl nucleoside subunits having 2'-hydroxyl moieties thereon.

69. A mammalian ribonuclease of claim 68 wherein said subunits of said compound are joined by phosphorothioate internucleoside linkages or phosphodiester internucleoside linkages.

70. A mammalian ribonuclease of claim 68 wherein said subunits of said first segment of said compound are joined by phosphorothioate internucleoside linkages.

71. A mammalian ribonuclease of claim 70 wherein said subunits of said second segment of said compound are joined by phosphodiester internucleoside linkages.

72. A mammalian ribonuclease of claim 70 wherein said subunits of said second segment of said compound are joined by phosphorothioate internucleoside linkages.

73. A mammalian ribonuclease of claim 68 wherein said subunits of said first segment of said compound are 2'-O-alkyl nucleoside subunits.

74. A mammalian ribonuclease of claim 68, wherein:

(A) said activity is inhibited by NaCl;

(B) said activity requires Mg++; and

(D) said mammalian ribonuclease has an apaprent molecular weight, as determined by SDS-PAGE, of about 50 to about 80 kilodaltons.

75. A mammalian ribonuclease of claim 68, wherein said ribonuclease is isolated from nucleii.

76. A mammalian ribonuclease of claim 68, wherein said ribonuclease is isolated from cytosol.

77. The mammalian protein of claim 68, wherein said ribonuclease is isolatable from human cells or tissues.

78. A double-stranded RNA substrate comprising a duplex of a first oligonucleotide and a second oligonucleotide, wherein

(A) said first and said second oligonucleotide each have a central portion having at least four consecutive ribofuranosyl residues having phosphodiester linkages, wherein said central portions are base-paired with each otehr in said duplex;

(B) at least one of said first and said second oligonucleotides have portions flanking said central portions having chemical modifications which make them resistant to single-stranded nucleases.

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79. A double-stranded RNA substrate comprising a duplex of a first oligonucleotide and a second oligonucleotide, wherein

(A) said first and said second oligonucleotide each have a central portion having at least four consecutive ribofuranosyl residues having phosphodiester linkages, wherein said central portions are base-paired with each otehr in said duplex;

(B) at least one of said first and said second oligonucleotides have portions flanking said central portions having chemical modifications which make them resistant to single-stranded

nucleases and increase their affinity for the otehr oligonucleotide of the duplex.

80. A double-stranded RNA substrate of claim 78, wherein said chemical modifications are phosphorothioate linkages or 2'-methoxy modifications.

81. An affinity matrix comprising the dsRNA substrate of claim 78.

82. A method of purifying a ribonuclease or non-degradative RNA-binding protein comprising contacting a sample containing said ribonuclease or non-degradative RNA-binding protein with the affinity matrix of claim 81.

83. A synthetic oligomeric compound comprising, in sequence;

a first segment having a plurality of 2'-O-alkyl nucleoside subunits being joined by phosphorothioate internucleoside linkages; and

a second segment having at least four consecutive 2'-hydroxyl ribonucleoside subunits being joined by phosphorothioate internucleoside linkages or by phosphodiester internucleoside linkages.

84. A compound of claim 83 further comprising a third segment having a plurality of 2'-O-alkyl nucleoside subunits being joined by phosphorothioate internucleoside linkages, said second segment being positioned in said oligomeric between said first and said third segments.

85. A compound of claim 83 wherein said second segment has phosphodiester internucleoside linkages.

86. A compound of claim 83 wherein said second segment has phosphorothioate internucleoside linkages.

87. A synthetic oligomeric compound comprising, in sequence;

a first segment having a plurality of 2'-O-alkyl nucleoside subunits being joined by phosphorothioate internucleoside linkages;

a second segment having at least four consecutive 2'-hydroxyl ribonucleoside subunits joined by phosphorothioate internucleoside linkages or by phosphodiester internucleoside linkages, and

a third segment having a plurality of 2'-O-alkyl nucleoside subunits being joined by phosphorothioate internucleoside linkages.

88. A compound of claim 87 wherein said second segment has phosphorothioate internucleoside linkages.

89. Use of said ribonuclease of claim 68 for treating an organism having a disease characterized by the undesired production of a protein encoded by said mRMA.

90. Use of said ribonuclease of claim 68 for identifying one of said mRNA or a protein encoded by said mRNA.

91. Use of said ribonuclease of claim 68 for diagnosing an aberrant state in an organism associated with a protein encoded by said mRNA.

92. A mammalian ribonuclease having the activity of catalyzing the degradation of a double stranded substrate wherein one of said strands of said substrate is a mRNA and the other of said strands comprises a compound of claim 1.

93. A double-stranded RNA substrate of claim 78, wherein one of said oligonucleotides has the nucleotide sequence of SEQ ID NO:8.